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REPRINTED FROM THE AMERICAN JOURNAL OF PHYSIOLOGY
Vol. 95, No. 2, November, 1930

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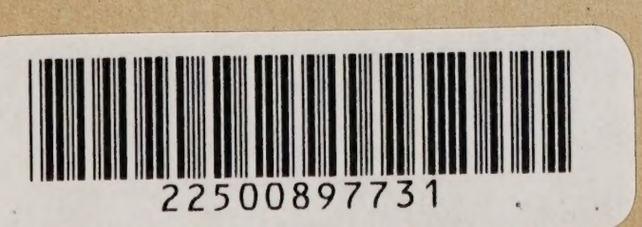

Reprinted from The American Journal of Physiology
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CIRCULATORY CHANGES DURING PERIODIC BREATHING PRODUCED BY MODERATE OBSTRUCTION TO THE CEREBRAL ARTERIES[1,2]

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Received for publication August 20, 1930

The study of periodic ventilation has been approached from many viewpoints. Perhaps the first clear reference to the condition as observed in man was that given by Hippocrates (Adams, 1849) when he described, what we now know to be periodic breathing, in the following words, "The respiration throughout like that of a person recollecting himself, was rare and large." Since the time of Hippocrates a large number of papers have appeared dealing with this phase of ventilation. It is not within the scope of the present paper to review the numerous theories and experimental data which have a bearing on this peculiar respiratory phenomenon. However, we would like to call particular attention to some of those works which have a more or less direct bearing on the present study. One of the outstanding of these is that of Eyster (1906), who by means of increased intracranial pressure experimentally induced excellent examples of periodic breathing. He pointed out that, "A sudden increased supply of blood to a respiratory center which has its irritability considerably depressed as the result of long continued insufficient blood supply, but is nevertheless still capable of response, may result in apnea;" and that "Cheyne-Stokes respiration in states of increased intracranial tension, with blood pressure waves rising and falling above and below the line of intracranial tension, is due to periodic activity of the respiratory, vasomotor, and cardio-inhibitory centers, the underlying cause of which is an alternate anemia and blood supply to the medullary centers."

Douglas and Haldane (1909) after experiments on man and animals with overventilation or breathing through a long tube with or without a soda lime cartridge, came to the conclusion that, "Periodic breathing is produced by the periodic occurrence and disappearance of the excitatory effects of want of oxygen on the respiratory center. The want of oxygen may be due to abnormal deficiency in the alveolar oxygen pressure or it

[1] Preliminary report appeared in the Proceedings of the Society for Experimental Biology and Medicine, 1929, xxvi.

[2] A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

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may be due to effects in the circulation, or changes in the breathing or to both causes combined."

Macleod (1921) induced periodic breathing in decerebrate cats by a number of procedures which included the periodic compression of the vertebral arteries. He pointed out that, "The arterial blood pressure exhibited waves synchronous with those of the respirations, and occasionally there is evidence of vagus slowing of the heart during the rising part of the curves. The arterial waves are often relatively much more pronounced than the respiratory and occasionally the former may be marked without any detectable periodicity of breathing."

The emphasis placed by Gesell (1923) on the significance of the volume flow of blood in relation to the metabolism, the state of oxidation, and the acid base equilibrium of the respiratory center as effected by the transport of oxygen and carbon dioxide of the blood, suggested a more detailed experimental analysis of periodic respiration.

As far as we have been able to ascertain, the exact nature of blood volume flow changes during periodic breathing has not been determined. In order to gain a clearer conception of this relationship, blood volume flow was measured not only to the brain but to other parts of the body as well, to correlate peripheral and central changes.

Method. Dogs anesthetized with morphine and urethane were used for all experiments. Unless otherwise stated, 0.5 cc. of a 2 per cent solution of morphine and 1 gram of urethane per kilogram of body weight was used. Periodic breathing was induced in all cases by limiting the cerebral flow of blood. This was accomplished by the gradual occlusion of the carotid and vertebral arteries. The blood of one of these arteries, before reachng the head, passed through a compression chamber which is illustrated in figure 1. This consists of an inner rubber tube, *C*, surrounded by a *T* shaped glass tube. The rubber tube was prepared by cementing together the edges of two strips of rubber dam. The circulating blood passed through this tube. A mercury manometer arranged to record the pressure in the glass chamber is in series with *A* and a Mariotte bottle. When pressure is applied, the outflow *B* is closed. Roughly speaking, if the pressure in the chamber surrounding tube *C* is higher than the mean blood pressure, the walls of tube *C* are pressed tightly together without wrinkling and allow no blood to pass. It follows, therefore, that during rhythmical waves in blood pressure which rise above and fall below the occlusion pressure, periodic variations in blood flow to the head occur. The compression chamber, therefore, supplies us with a method for readily controlling blood flow to the head without the introduction of a foreign fluid into the subdural spaces or increasing the volume of blood from the absorption of the compression fluid which is used to increase the intracranial pressure. These changes in blood flow are similar in many respects to those obtained

by the intracranial pressure method employed by Eyster (1906). When arterial compression is used, only one arterial flow is automatically controlled. The remaining arteries are occluded or deoccluded as the conditions demand.

The thermoelectric method of Gesell and Bronk (1926) was employed for measuring the blood volume flow changes in the arterial streams. It was found desirable, on account of the importance of time relationships, to resort to a very small thermopile vessel. This reduces the lag between blood flow changes and thermopile response. Figure 2 is a sectional view of the thermopile vessel which was interposed between the heart and compression chamber. It differs from a modification described by Gesell (1929), in the absence of an outer vacuum jacket and its marked reduction in size. The thermopile was attached at *A* and *B*, one side being employed for the cold junctions and the other for the hot. The inner tube *C* is a very thin glass tube through which the arterial stream flows. The distance between *A* and *B* is 25 mm. and the outer jacket for water which surrounds

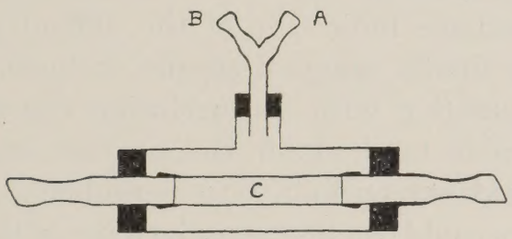


Fig. 1

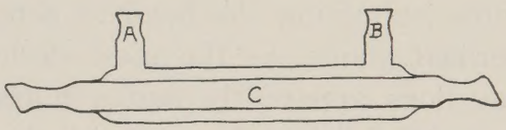


Fig. 2

tube *C* is only 7 mm. in diameter. Allowing water from a Mariotte bottle to flow through at the rate of 20 cc. per minute, the lag of the instrument was found to be about 4 seconds. On all the records an upstroke indicates an increased blood flow and a down stroke a decreased flow. Any line marked *X* signifies mechanical adjustment of the writing point to keep it on the record. A type K Leeds and Northrup potentiometer was employed and connected in the usual manner by thread and pulley to the writing point. In figures 3A, 3B, and 3C, the coarse adjustment of the potentiometer was used, but for figures 4A, 4B, 4C, 4D, and 4E, the fine setting was used. The fine setting was especially desirable for recording the small variations in flow of the femoral artery, as it increased the sensitivity ten times.

The venous returns of the external jugular, vertebral, and femoral veins was measured by the enclosed drop method of Gesell (1929). This method has the distinct advantage of allowing automatic return of the blood to the vein and at the same time keeps the blood volume constant. It is desirable to have as many drops as possible per minute in order to record the smallest variations in volume flow. Therefore, the smallest sized drop compatible

with the extent of the volume flow was employed in each vein. For example, in the femoral vein, a very small drop was used since the flow was not rapid, but a much larger drop was required in the external jugular vein where a large volume of blood was flowing. To prevent clotting, 40 mgm. of heparin per kilogram of body weight were used. This was injected at the beginning of the experiment, the heparin being dissolved in about 50 cc. of warm isotonic saline. When the enclosed drop method was used, partial defibrination of the blood before the addition of the heparin tended to prevent streaming of the blood through the oil. This partial defibrination was accomplished by means of small hemorrhages and reinjection. In the case of a very small intestinal vein, the external drop method was used and recording accomplished through a system of tambours.

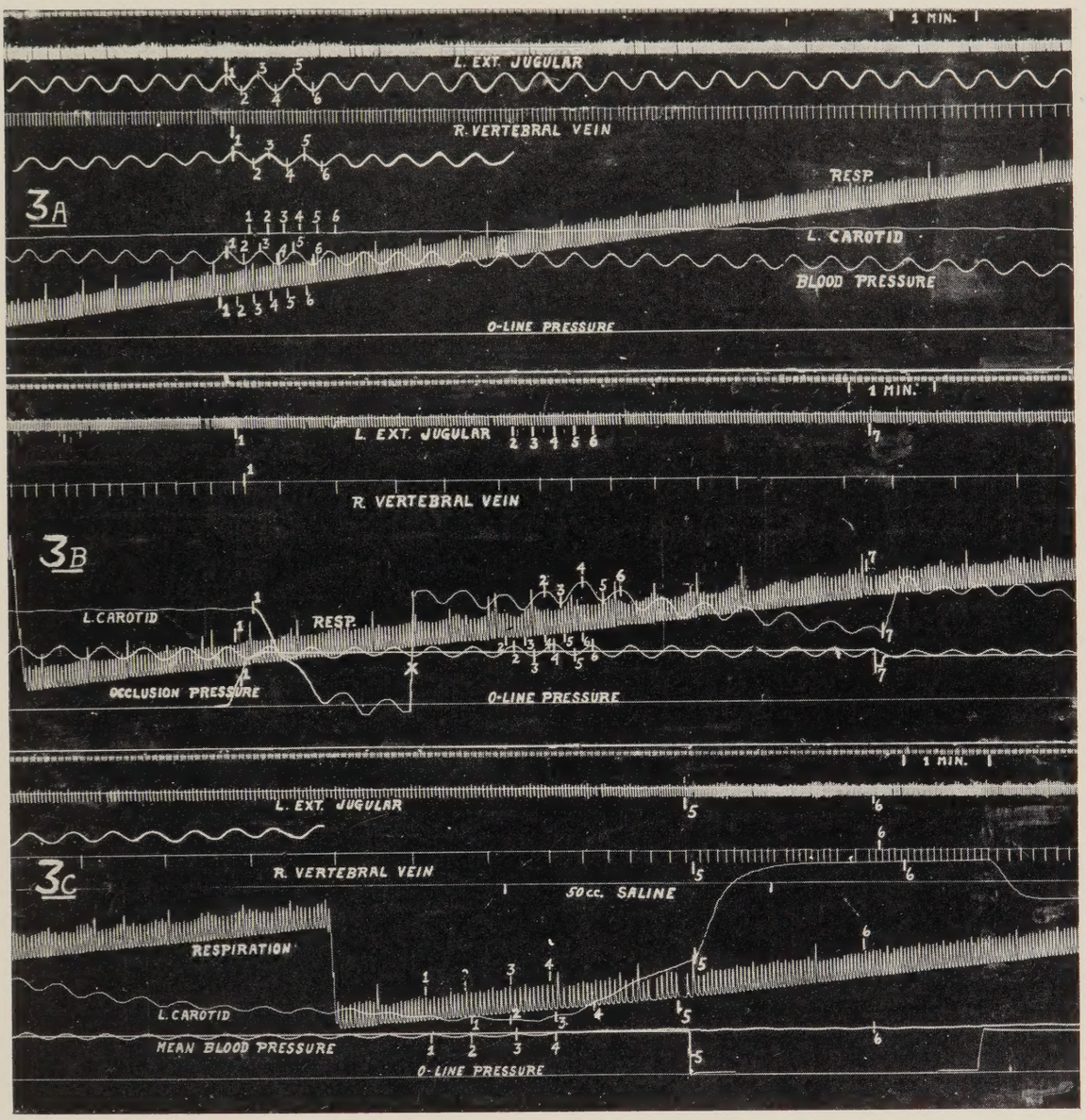
Blood pressure, ventilation, oxygen consumption, and time were simultaneously recorded with the blood volume flow changes. Corresponding points on these different measurements are designated by the corresponding numbers on the figures.

Results. A study of the literature reveals a surprising number of experimental procedures which is perhaps indicative of the difficulty in producing periodic ventilation. We finally adopted simple occlusion of arteries supplying the head in conjunction with the occlusion chamber described above, as the most desirable method for the present study. Some dogs apparently had a marked susceptibility to periodicity. If respiration failed in these animals they could usually be revived by artificial ventilation and deocclusion of the arteries supplying the head. Upon curtailing the blood flow to the head, periodic ventilation frequently returned.

As a result of our experiments, we have found periodic ventilation to fall into two distinct types. One type is characterized by rhythmical changes in depth and rate of respiration without apneic periods. This type is considered in this paper. The other type which will be fully considered in the second paper, has distinct apneic periods varying from a few seconds to two minutes or more in duration and is produced by greater impairment of circulation.

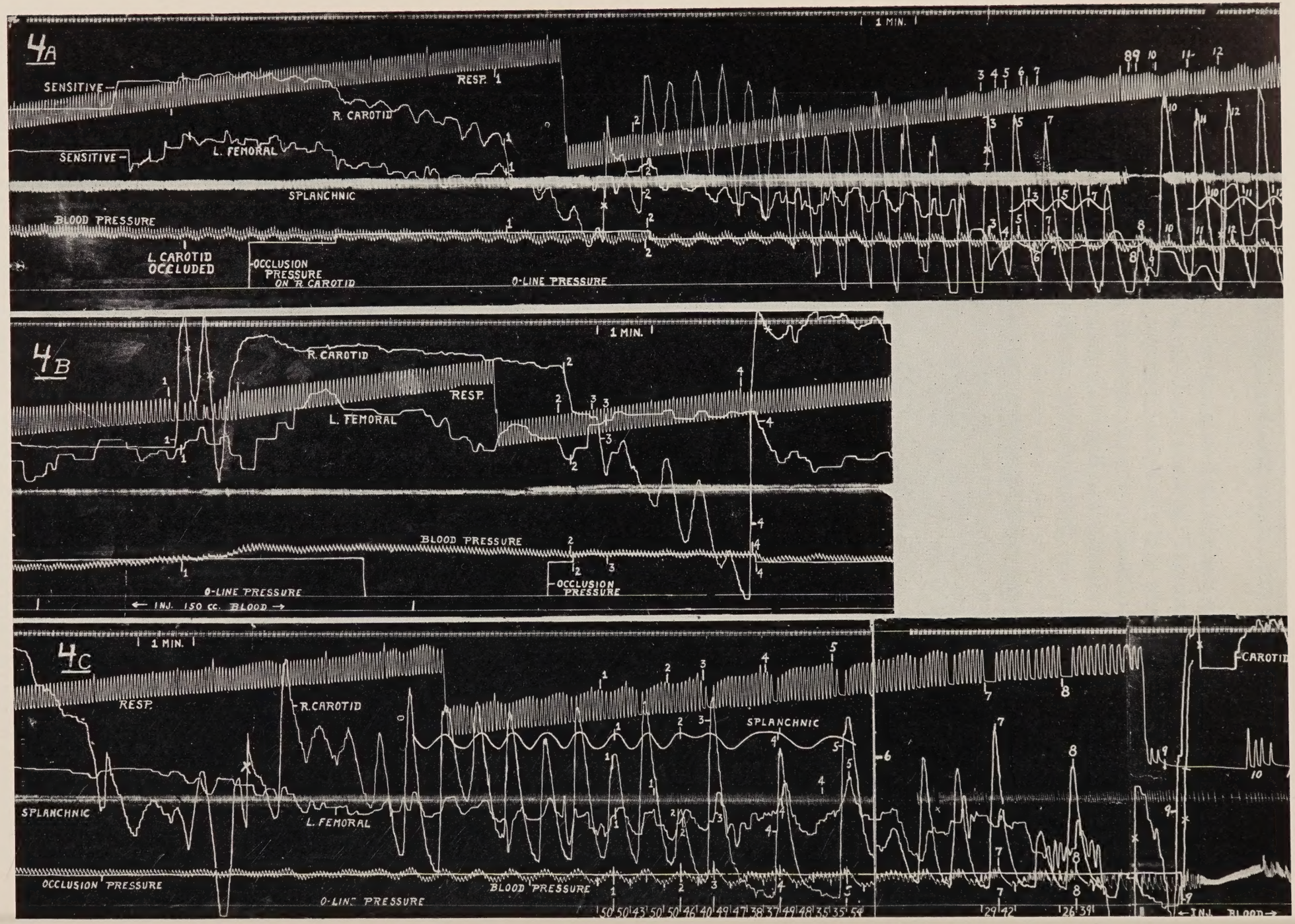
Figures 3A, 3B, and 3C represent a series of records in which several blood flows were measured. The vertebral arteries, the left vertebral vein, the right external jugular vein, were occluded before any records were taken. The right common carrotid artery was patent during the entire experiment. The blood in the left common carotid artery flowed through the thermopile vessel and the compression chamber before reaching the head. The venous returns of the left external jugular and right vertebral veins were followed by the enclosed drop method. The flow of blood of the right vertebral vein was returned to the heart through the right external jugular vein which was peripherally occluded.

We do not know when periodicity first occurred in this experiment as it was present at the beginning of the first record (fig. 3A) and occurred without application of pressure to the left carotid artery. In figure 3A, below the records of the flows of blood of the left external jugular vein and right vertebral vein, periodic variations in flow were diagrammatically plotted. A careful inspection of the thermoelectric record of the left common



Figs. 3A, 3B, 3C

carotid arterial flow revealed only slight rhythmical variations. These waves although very small represent significant variations in flow as the coarse adjustment of the potentiometer was used. As indicated by the corresponding numbers, 1, 3, and 5, the highest venous and arterial flows all occurred at the crests of the mean blood pressure waves. At the troughs of the mean blood pressure waves 2, 4, and 6, the lowest arterial and venous flows occurred. Respiration had a very smooth even periodicity through-


4A
1 MIN.
SENSITIVE
RESP.
R. CAROTID
SENSITIVE
L. FEMORAL
SPLANCHNIC
BLOOD PRESSURE
L. CAROTID OCCLUDED
OCCLUSION PRESSURE ON R. CAROTID
0-LINE PRESSURE
4B
1 MIN.
R. CAROTID
RESP.
L. FEMORAL
BLOOD PRESSURE
0-LINE PRESSURE
OCCLUSION PRESSURE
← INJ. 150 CC. BLOOD →
4C
1 MIN.
RESP.
R. CAROTID
SPLANCHNIC
L. FEMORAL
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0-LINE PRESSURE
BLOOD PRESSURE
CAROTID
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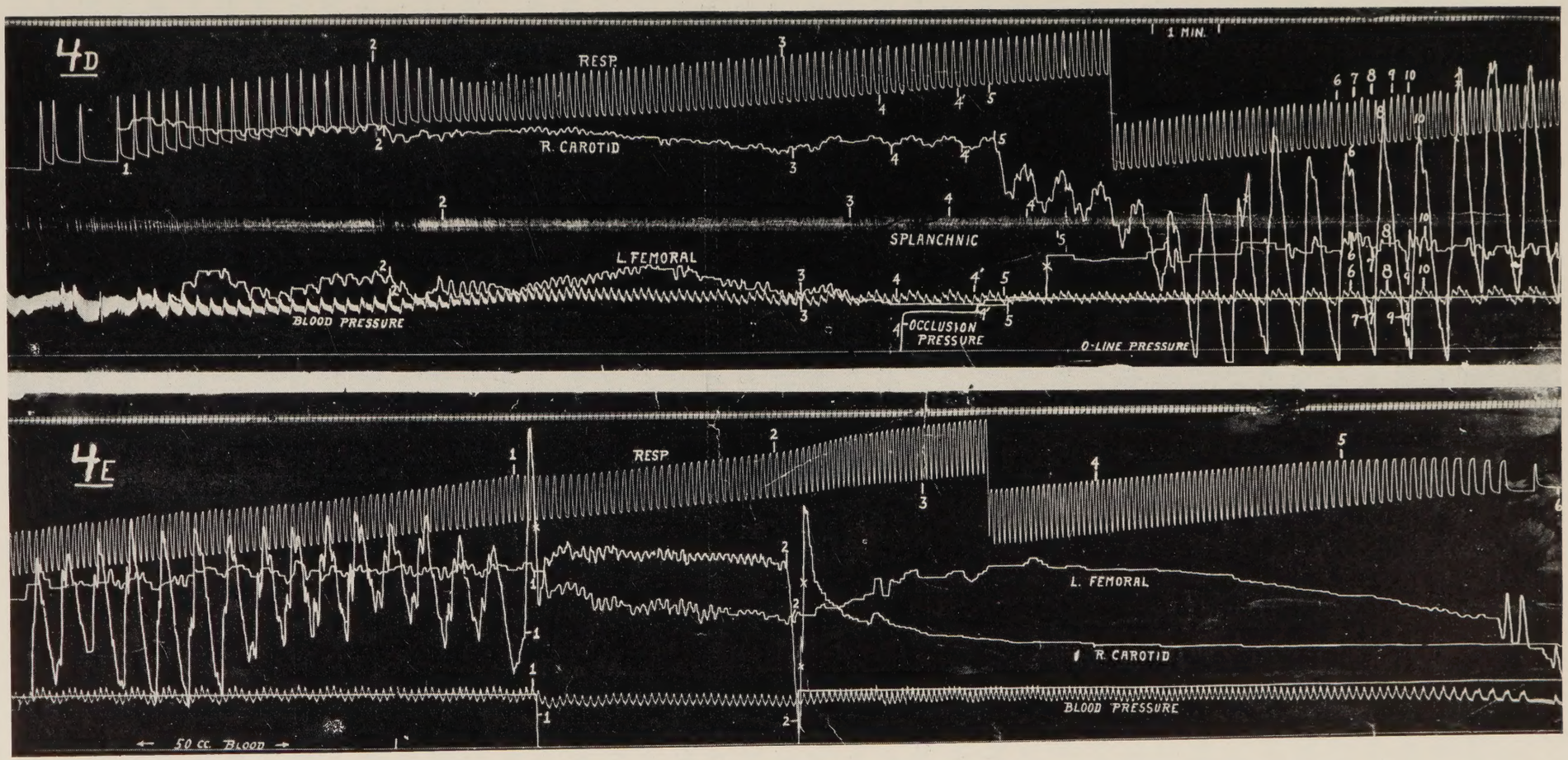
4D
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1 MIN.
R. CAROTID
SPLANCHNIC
L. FEMORAL
BLOOD PRESSURE
OCCLUSION PRESSURE
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4E
RESP
L. FEMORAL
R. CAROTID
BLOOD PRESSURE
← 50 cc. BLOOD →

Figs. 4D, 4E

out this figure, with the lowest depth and slowest rate occurring a few seconds after the highest blood pressures and blood flows. This relationship appeared through this experiment. The vertebral venous flow soon became too slow to show changes in periodicity accurately. The gradual fall in blood pressure was accompanied by a slowing of the venous returns of the left external jugular and right vertebral veins as well. Periodicity of the recorded vertebral flow was plotted only up to the middle of figure 3A.

At number *1* in figure 3B, the left carotid was partially occluded by increased pressure in the compression chamber. The thermoelectric record of the arterial flow showed a decreased volume flow. This same decrease in flow occurred in the right vertebral and left external jugular veins. The depth of respiration gradually increased following compression number *1*. This was followed by an increased periodicity of ventilation during which the same relationship existed between blood pressure and blood flow and respiration as pointed out in figure 3A. Thus respiration shows the lowest depth and rate following the highest arterial pressures and flows *2*, *4*,and *6*, and the highest depth and rate at the lowest arterial pressures and flows *3* and *5*. Oxygen consumption was only slightly less in this figure than in figure 3A. This was shown by the smaller rise in the base line of respiration. Total ventilation was increased approximately 25 per cent by the application of the occlusion pressure. In other words, the general metabolism of the body had not changed materially but the respiratory center was manifesting a local stimulation associated with diminished blood pressure and blood flow.

At *7* the occlusion pressure was slightly lowered as the crests of the blood pressure waves were failing to rise appreciably above the line of occlusion pressure. A significant increased carotid flow took place which was associated with a temporary decrease in respiration.

During the first half of figure 3C, blood pressure waves were slight as compared with those in figure 3A. The carotid flow, likewise manifested a decrease in amplitude of the waves and the level of flow slowly fell. Periodicity in respiration was very much diminished at *1* and *2*. The slow injection of saline at *3* brought about a definite decrease in ventilation as soon as the mean blood pressure rose above the occlusion pressure. Removal of occlusion at *5*, increasing the volume flow of blood still more, was followed first by a short apnea which then gave way to increased ventilation indicative of a general recovery of the respiratory center.

Figures 4A, 4B, 4C, 4D, and 4E show the results of another experiment. Both vertebral arteries were permanently occluded. Thermopile vessels were interposed in the blood flows of the right common carotid and left femoral arteries. Variations in flow were followed in each by the sensitive setting of the potentiometer. One of the smaller intestinal veins was can-

nulated for recording the flow of blood by the external drop method. The blood was not defibrinated, only heparin being used to prevent clotting.

This animal developed periodic breathing to a marked degree. The beginning of the record is shown in figure 4A. Occlusion of the left common carotid had no influence on respiration but waves in blood pressure developed. The slow continuous hemorrhage entailed by recording the splanchnic flow of blood in itself decreased mean blood pressure and cerebral blood flow and may be partly responsible for the development of periodicity. Further occlusion of the right carotid brought on larger oscillations in blood pressure and volume flow of blood but did not bring on an immediate change in respiration. As the mean blood pressure fell below the occlusion pressure at *1*, the flow in the right carotid sharply decreased. The femoral flow, however, exhibited only a gradual decline. At *2* a slight lowering of the occlusion pressure brought about a marked increase in carotid flow which was associated with a slight decrease in respiration. Femoral flow decreased slightly. This was probably due to the fall in mean blood pressure. With the establishment of this new level in occlusion pressure, waves in blood pressure became very marked. The variations in carotid flow were of great magnitude. The irregular respiration became distinctly periodic at *3*. The relation of respiration to blood flow and mean blood pressure is shown by the corresponding numbers *3*, *4*, *5*, *6*, and *7*. Both femoral and splanchnic flows were greatest at the crests of the blood pressure waves and ventilation was the smallest. A small increase in carotid flow at *8* was associated with only a slight decrease in the rate and depth of respiration. At *9*, a lowering of the occlusion pressure was accompanied by a larger increase in flow of blood and a greater depression of ventilation. Following this the oscillations in volume flow became larger despite the fact that the oscillations in mean blood pressure were smaller. These changes were associated with a more marked periodicity in ventilation.

During the time required to change smoked papers, mean blood pressure had fallen below the line of occlusion pressure and prominent waves in blood pressure and respiration had disappeared. This condition is seen at the begininng of figure 4B. A slow injection of the blood was begun at the extreme left of the figure and just prior to *1*, ventilation gradually diminished along with the increased blood pressure and blood flow to the medullary centers presumably by way of the spinal anastomoses. At *1*, when mean blood pressure was high enough to overcome the pressure in the occlusion chamber, a large carotid blood flow occurred. Immediately following this, there was a marked decrease in ventilation which then gave way to an even ventilation. At *2*, the occlusion pressure was raised again to equal the mean blood pressure. Femoral flow increased considerably although there was only the slightest increase in mean blood pressure.

Coincident with this there was a marked reduction in carotid flow, but no appreciable change in ventilation. From *3* to *4* there were slight waves in mean blood pressure which were associated with moderate variations in carotid flow. Although slightly more irregular, respiration did not show distinct periodicity. Partial de-occlusion of the carotid at *4* was accompanied by increased carotid flow of blood, decreased mean blood pressure and decreased ventilation. With a gradual deterioration of the animal there was a gradual fall in mean blood pressure which automatically increased the occlusion of carotid artery in record 4C with the new occlusion pressure established at *4* in record 4B. When the occlusion pressure and mean blood pressure began to coincide periodicity was established and became more pronounced as the mean blood pressure fell and as the animal continued to deteriorate. Toward the close of the record pulse rate became periodic and apneas appeared. The results began to resemble more closely those produced by marked impairment of circulation described in the following paper.

Between figures 4C and 4D, seven minutes elapsed during which the respiration was irregular. At number *1* of figure 4D this irregularity suddenly changed to very deep regular breathing. At *2* the left carotid was de-occluded and within the next minute respiratory rate increased and depth decreased. Re-occlusion was begun at *4*. There were no immediate effects until the occlusion pressure was equal to the mean arterial pressure, *5*. Then periodicity in mean blood pressure and carotid flow was established and as the periodic changes in mean blood pressure and carotid flow of blood increased in magnitude they were associated with greater changes in ventilation. De-occlusion at *1* in record 4E results in a general decrease in ventilation and re-occlusion at *2* in a general increase. There is then a gradual impairment of respiratory function which presumably may be attributed to the reduction in cerebral flow of blood, attempts at resuscitation by injection of blood failed.

Discussion. Granting that the activity of the respiratory center is sensitive to changes in volume flow of blood by virtue of chemical changes occurring in the center the periodic changes in ventilation have a simple explanation in the changes in cerebral flow which are here definitely demonstrated to exist. It is only essential to apply the principles of chemical stimulation of the respiratory center to the circulatory centers (Gesell, 1929) to complete the explanation. But the recent findings of Heymans and Bouckaert (1930) demonstrating depression of respiratory movements with increased pressure in the carotid sinus suggest that reflexes initiated by alternate stretching and contraction of the carotid sinuses and arch of the aorta might well play a part in the periodicity of ventilation, perhaps even be self sustaining in maintaining periodicity in circulation and respiration. The relative importance of central chemical and peripheral vascular reflex effects during periodicity requires further study.

SUMMARY.

Periodic breathing was induced in dogs under morphine and urethane anesthesia by moderate occlusion of the cerebral blood vessels. This was accomplished by placing one of the common carotid arteries in a compression chamber, thus making possible partial or complete occlusion of this artery. The remaining cerebral arteries were occluded and de-occluded as conditions required.

Pulmonary ventilation and mean blood pressure were recorded. Volume flow of blood was followed in the carotid and femoral arteries thermoelectrically with small thermopile vessels of short lag. The vertebral and external jugular venous flows were recorded by the enclosed drop method and intestinal venous flow by the external drop method.

Periodic changes occurred in mean blood pressure, in femoral and carotid arterial blood flows, in vertebral, external jugular, and splanchnic venous flows, and in depth and rate of respiration. Changes in blood flows were synchronous with the periodic variations in mean blood pressure. In contrast to this general periodicity there were no obvious rhythmical changes in heart rate. Ventilation increased during decreasing blood pressures and blood flows, and decreased with increasing pressures and flows. With the conditions provided no apneas developed.

The absence of periodic changes in heart rate suggested that the changes in mean blood pressure may be due to periodic activity of the vasomotor center.

It is concluded that the periodic changes in ventilation are related to the periodic changes in the circulatory system but since volume flow of blood and mean blood pressure vary with each other the periodic changes in ventilation may be a result of periodic chemical changes in the respiratory center produced by fluctuations in blood flow or to the reflex effects of periodic stretching and contraction of the aorta and of the carotid sinus. In the absence of crucial experiments the relative importance of these two effects cannot be evaluated.

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